IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Klaus BOSSLET *et al.* Examiner: Elli Peselev

Serial No.: 10/728,098 Group Art Unit: 1623

Filed: December 5, 2003 Confirmation No.: 7295

Title: EFFECTOR CONJUGATES, METHODS FOR THEIR PREPARATION AND THEIR PHARMACEUTICAL USE

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

This is an appeal from the decision of the Examiner finally rejecting claims rejections of claims 1-10, 12 and 23-33 of the above-identified application.

(I) REAL PARTY IN INTEREST

The real party in interest in the present application is Bayer Schering Pharma, successor to Schering AG, to whom an assignment of the present application is recorded at Reel 015306, Frame 0762.

(II) RELATED APPEALS AND INTERFERENCES

Copending application Serial Number 09/485,292 is also on appeal.

(III) STATUS OF THE CLAIMS

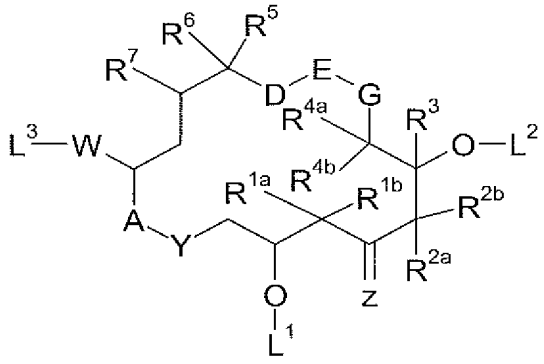
Claims 1-10, 12 and 23-33 are pending in the application. Each of these claims is on appeal. Claims 11 and 13-22 have been canceled.

(IV) STATUS OF AMENDMENTS

No Amendments were presented subsequent to the Final Rejection.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

The invention is directed, in claim 1, to a conjugate compound of formula (I):



I,

in which

R^{1a} and R^{1b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_m-$ group, in which m is 2 to 5,

R^{2a} and R^{2b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_n-$ group, in which n is 2 to 5, or C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl,

R^3 is hydrogen, C_1-C_{10} alkyl, aryl or aralkyl, and

R^{4a} and R^{4b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_p-$ group, in which p is 2 to 5,

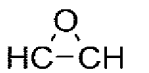
R^5 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, CO_2H, CO_2alkyl, CH_2OH, CH_2Oalkyl, CH_2Oacyl, CN, CH_2NH_2, CH_2N(alkyl, acyl)$_{1,2}$, or CH_2Hal,

Hal is a halogen atom,

R^6 and R^7, in each case, are hydrogen, or together an additional bond or together an oxygen atom, or together an NH group, or together an N-alkyl group, or together a CH_2 group, and

G is an oxygen atom or CH_2,

D-E is a group H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2,

CH_2-CH(OH),  , O-CH_2, or, if G represents a CH_2 group, is additionally CH_2-O,

W is a group C(=X)R^8, or a bi- or tricyclic aromatic or heteroaromatic radical,

L^3 is hydrogen, or, if a radical in W contains a hydroxyl group, optionally forms a group O-L^4 with the latter, or, if a radical in W contains an amino group, optionally forms a group NR^{25}-L^4 with the latter,

R^{25} is hydrogen or C_1-C_{10} alkyl,

X is an oxygen atom, or two OR^{20} groups, or a C_2-C_{10} alkylenedioxy group, which is straight-chain or branched, or H/OR^9, or a $CR^{10}R^{11}$ group,

R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen or CN, and

R^9 is hydrogen or a protective group PG^X,

R^{10} and R^{11}, in each case independently of one another, are hydrogen, C_1-C_{20} alkyl, aryl, or aralkyl, or together with a methylene carbon atom form a 5- to 7-membered carbocyclic ring,

Z is oxygen or H/OR^{12},

R^{12} is hydrogen or a protective group PG^Z,

A-Y is a group O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) or NR^{21}-SO_2,

R^{20} is C_1-C_{20} alkyl,

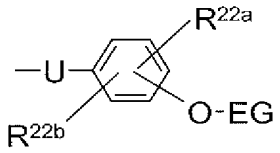
R^{21} is a hydrogen atom or C_1-C_{10} alkyl,

PG^X, PG^Y, and PG^Z are a protective group PG, and

L^1, L^2, L^4, independently of one another, are hydrogen, a group C(=O)Cl, a group C(=S)Cl, a group PG^Y or a linker-recognition unit of formula (III);

with the condition that at least one substituent L^1, L^2 or L^4 represents a linker-recognition unit of formula (III);

the linker-recognition unit of formula (III) has the following structure,



III,

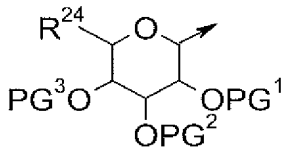
in which

R^{22a} and R^{22b}, independently of one another, are hydrogen, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy, aryl, aralkyl, hydroxy, alkoxy, CO_2H, CO_2alkyl, halogen, CN, NO_2, NH_2, or N_3,

U is $-C(=O)NR^{23}-$, $-C(=S)NR^{23}-$, $-C(=O)NR^{23}-CH_2-$, $-C(=S)NR^{23}-CH_2-$, $-C(=O)O-$, $-C(=S)O-$, $-C(=O)O-CH_2-$, or $-C(=S)O-CH_2-$,

R^{23} is hydrogen or C_1-C_{10} alkyl, and

EG is a recognition unit of formula (IV):



IV,

in which

R^{24} is a group CH_2OPG^4 or a group CO_2R^{26},

PG^1, PG^2, PG^3, and PG^4, independently of one another, are hydrogen or a protective group PG,

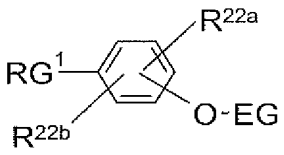
R^{26} is hydrogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_4-C_7 cycloalkyl, which can contain an oxygen atom, aryl, aralkyl, tris(C_1-C_{20} alkyl)silyl, bis(C_1-C_{20} alkyl)-arylsilyl, (C_1-C_{20} alkyl)-diarylsilyl, or tris(aralkyl)-silyl,

as a uniform isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof. See Appellants' specification at page 2, line 24 through page 6, line 7. The invention is also directed, according to claim 12, to a process for the production of a conjugate compound according to claim 1, which comprises reacting:

a compound of formula (I), in which the substituents have the meanings that are

mentioned in claim 1, but the condition that at least one substituent L^1, L^2, or L^4 represents a linker-recognition unit of formula (III) need not be met, and at least one substituent L^1, L^2, or L^4 represents hydrogen, a group C(=O)Cl or a group C(=S)Cl,

with a linker-recognition unit, which is selected from the group that consists of:
a linker-recognition unit of formula (III^1)

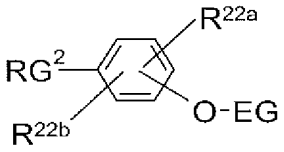


III^1,

in which

RG^1 represents an O=C=N group or an S=C=N group or an O=C=N-CH_2 group or an S=C=N-CH_2 group; and

R^{22a}, R^{22b} and EG have the meanings that are mentioned in claim 1; or
a linker-recognition unit of formula (III^2):



III^2,

in which

RG^2 represents an HO-CH_2 group or an HNR^{23}-CH_2 group; and

R^{22a}, R^{22b} and EG have the meanings that are mentioned in claim 1;
but with the condition that the following compounds are not included:

(4-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(2-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(4-Hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(2-Hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(4-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside;

(2-Hydroxymethyl-4-nitro)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

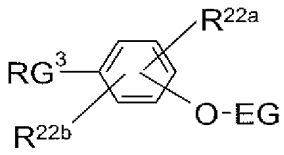
(4-Hydroxymethyl-2-nitro)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(2-Hydroxymethyl-4-nitro)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(4-Hydroxymethyl-2-nitro)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(2-Chloro-4-hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside; and

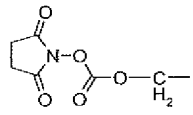
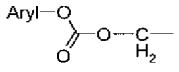
(2-Chloro-4-hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester; or a linker-recognition unit of formula (III^3):



III^3,

in which

RG^3 represents a Hal-C(=O)-CH_2 group or a Hal-C(=S)-CH_2 group or an R^{27}-C(=O)-O-C(=O)-CH_2 group or an R^{27}-C(=O)-O-C(=S)-CH_2 group or a

 group or a  group;

R^{27} is C_1-C_{10} alkyl, aryl or aralkyl; and

R^{22a}, R^{22b} and EG have the meanings that are mentioned in claim 1;

but with the condition that the following compounds are not included:

2,5-Dioxopyrrolidin-1-yl-[4-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[4-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)-methyluronate)benzyl]carbonate;

4-Nitrophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-benzyl]carbonate;

4-Nitrophenyl-[2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-5-nitrobenzyl]carbonate;

4-Nitrophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate;

4-Nitrophenyl-[4-methoxy-5-nitro-2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)benzyl]carbonate;

4-Nitrophenyl-[4-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate; and

4-Chlorophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate. See Appellants' specification at page 34, line 11 through page 35, line 2.

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection for consideration on appeal are the rejection of claim 33 under 35 U.S.C. §112, first paragraph, and the rejection of claims 1-10, 12 and 23-33 under 35 U.S.C. §112, first paragraph.

(VII) ARGUMENT

Rejection of Claim 33 Under 35 U.S.C. 112, First Paragraph

Claim 33 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. It is argued, on page 2 of the Final Rejection, that there is no written description of "m is 3 to 5" in the specification. Appellants' specification defines m, in formula I, as "2 to 5", see page 3, line 4. It is thus clear, under applicable law, that this disclosure supports the narrowed range of 3 to 5. For example, the Federal Circuit's predecessor court has stated that a disclosure of 25 to 60 supported a later claimed range of 35 to 60, even in the absence of an explicit recitation of "35." The Court held that, in the area of numerical ranges, the disclosure of a broad range clearly teaches that Appellants invented, and thus described, all the values within the range. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Similarly, the Patent Office's own Board of Interferences held that a range of 10 to 79%, with preferred ranges of 40 to 79 and 40 to 60, supported a claim of 10 to 25%, although the value of "25" was nowhere explicitly recited. The board held that, in light of *In re Wertheim, supra*, "one of ordinary skill in the art, given [Appellants'] disclosure, would consider that use of the 10 to 25% range would be a part of [Appellants'] invention." See *McLaughlin v. Roberts*, 197 USPQ 831 (POBI 1978). Thus, the present disclosure of 2 to 5 clearly supports the claimed range of 3 to 5, and there exists more than ample basis to overturn the rejection.

The Advisory Action provides no amplification on the [incorrect] arguments of the Final Rejection, simply stating that the range of 2 to 5 cannot support "3" to 5 as there is no disclosure of "3". As explained amply above, a specific disclosure of the value of three is unnecessary.

Rejections of All Remaining Claims Under 35 U.S.C. 112, First Paragraph

Claims 1-10, 12 and 23-33 have been rejected under 35 U.S.C. 112, first paragraph, as

failing to comply with the enablement requirement. Appellants respectfully submit that this rejection is in error. The Final Rejection and Advisory Action both fail to provide substantive comment on the majority of the discussion provided by Appellants previously, e.g., in reply to the first Office Action.

Appellants maintain their position that the claimed compounds and methods of use are adequately enabled by the original disclosure when taken in view of the knowledge of one of ordinary skill in the art. Appellants maintain that, despite the disclosure in Nicolau (U.S. Patent No. 6,441,186) cited to support the rejection, the PTO has not sufficiently met its burden of refuting the inventors' statements in the application regarding how to make and use the invention. The burden lies first with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims; see, e.g., *In re Marzocchi et al.*, previously cited. In accordance with *Marzocchi*, the terms of the instant claims correspond in scope with the disclosure regarding the use of the compounds in "treating a disease associated with proliferative processes" (i.e., claim 24) and specific embodiments of such diseases (i.e., claim 25). See, e.g., the disclosure at page 6, last full paragraph, of the instant specification. Also, the terms of the instant claims correspond in scope with the disclosure regarding the use of the compounds in "treating a primary tumor and/or metastases that are not operatively accessible" (i.e., claims 26-28). See, e.g., the disclosure at the paragraph bridging pages 6-7 of the instant specification. The Final Rejection again relies upon Nicolau (as discussed further below) but still fails to provide an explanation of <u>*why*</u> it doubts the truth or accuracy of these and other statements of the inventors supporting the use of the claimed compounds. (The Advisory simply states that the rejection is maintained for the reasons set forth in the Final Rejection.) The reliance on Nicolau fails to provide a sufficient basis for any such assertion. The objective evidence of record and known to one of ordinary skill in the art, including Nicolau but considered with the other evidence already of record (e.g., U.S. Patent Nos. 6,982,276 and 7,008,936) is, in fact, supportive of the inventors' statements. See, e.g., the paragraph at the top of page 2 of the disclosure pointing out the knowledge in the art of the very high anti-proliferative activity of epothilone compounds, i.e., the class to which the structure of the effector part of the conjugate of formula (I) belongs. Such anti-proliferative activity of the epothilone class of compounds was well known to those of ordinary skill in the art; see, e.g., U.S. Patent Nos. 6,982,276 and 7,008,936, as just a sample of other references in the art.

The evidence in Nicolau alleged to contradict that Appellants' epothilone conjugate

compounds would be useful in treating diseases associated with proliferative processes and particularly for treating a primary tumor and/or metastases is not convincing on this point, particularly in view of the other evidence contradicting it. The general teaching of Nicolau considered as a whole is that epothilones and analogs thereof are expected to have high clinical value due to their toxicity against tumor cells. For example, Nicolau states (col. 1, lines 29-31): "Epothilones are reported to be about 2000-5000 times more potent than Taxol with respect to the stabilization of microtubules." Nicolau also states (Abstract) that: "Several of the analogs are demonstrated to have superior cytotoxic activities as compared to epothilone A or epothilone B." Further, Figures 22 and 23 show that all the epothilone analogs tested by Nicolau demonstrated activity in stabilizing microtubules and in inhibiting human cancer cell lines.

The Final Rejection clings still to the remote statement within Example 5 that "the 4,4-ethano-epothilones proved inactive." However, such statement is not supported by any actual data nor is it provided in any context to determine what was intended by "inactive." It also does not indicate to which 4,4-ethano-epothiolones Patentees are referring. Generally, activity profiles of related compounds provide a sliding scale of activity and the probability that a compound related to a compound which is highly active would exhibit absolutely no activity is low. Instead, in the absence of any actual data in Nicolau, one of ordinary skill in the art would have interpreted this statement as meaning that certain 4,4-ethano-epothilones did not meet the threshold assigned for assessing activity in that particular assay. One of ordinary skill in the art would have no basis to conclude from this isolated statement that the 4,4-ethano-epothilones would have no anti-tumor activity whatsoever. This is particularly the case when the other evidence of record – including the additional evidence discussed below – is considered, since Nicolau provides no actual data to support the statement. Despite clinging resolutely to Nicolau as the basis for its reasoning, the PTO fails absolutely to comment on the foregoing discussion. However, this failure to analyze the specific teaching of the reference underscores the implausibility of the argument built thereupon.

Additionally, Appellants have previously submitted, with their reply of January 26, 2007, further evidence supporting the activity of the epothilone compounds. Specifically, Appellants have provided a Declaration under 37 C.F.R. §1.132 (submitted initially in application Ser. No. 09/485,292) directed to epothilone derivative compounds and use thereof. While the declaration was submitted in the copending application for the purpose of showing the advantage of 10-ethyl or higher alkyl epothilone derivatives over the corresponding 10-methyl epothilones, the data

demonstrate that all the epothilone analogs tested exhibited significant levels of activity in a number of assays connected with anti-proliferative activity. The Final Rejection discounts this data, misapprehending the reason for its submission, arguing that none of the compounds tested is within the scope of the claimed compounds. However, the declaration was not offered as evidence of unexpected results. All of the tested compounds contain, at the position corresponding to the 4,4-position according to Nicolau's nomenclature, dimethyl substitution or spirocyclobutyl substitution. This is significant because the 4,4-ethano-epothilones alleged in Nicolau to be "inactive" fall intermediary between these two structures, i.e., the 4,4-ethano group is a spirocyclpropyl group which has the same number of carbons as the dimethyl analog but has the steric hindrance like the spirocyclobutyl analog and is the adjacent homolog thereto. In view of this evidence and the absence of any actual data in Nicolau, one of one of ordinary skill in the art would find it highly unlikely that Nicolau actually found or meant to imply complete absence of activity for the 4,4-ethano-epothilones. In view of this data in assessing the evidence as a whole, it is again urged that the PTO's burden of proof is not met.

Finally, even if Nicolau's statement were correct that some 4,4-ethano-epothilones are totally inactive, such would not support non-enablement for appellants' claims as a whole. First, Nicolau does not identify which 4, 4-ethano analogs it is referring to and certainly they did not test all of them. Further, the law is clear that the inclusion of a relatively small number of inoperative species within the generic scope of the claim does not render the claim invalid for non-enablement. See, e.g., Atlas Powder Co. v E.I. DuPont De Nemours & Co., 224 USPQ 409, 414 (Fed. Cir. 1984), stating:

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude .. possible inoperative substances.'

As held therein, only if the number of inoperative embodiments is significant does the possibility of invalidity arise. Nicolau does not indicate which specific 4,4-ethano analogs would allegedly be inoperative so no support is provided that a large number of them would be inoperative. In any event, this would only be a small portion of the scope of appellants' claims.

For all of the above reasons, it is urged that the PTO has not met its initial burden of proof of non-enablement and, at least for this reason, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The Final Rejection also again refers to four of the "Wands" factors in its discussion of

the enablement rejection. As previously noted, the *Wands* decision pointed to consideration of eight factors. It was previously stated to be assumed to be admitted that the other four factors not addressed in the office actions weigh in favor of enablement. The Final Rejection and Advisory Action do not dispute this. It is again emphasized that these factors are all considered together and, thus, one will not alone support lack of enablement. It is moreover clear that a balancing of all of these factors does not support a non-enablement rejection. Appellants have the following comments regarding each factor:

- Breadth of Claims - The scope of the methods treated is no broader than the acknowledged and known activity in the art of epothilones as anti-proliferatives. Appellants' invention recognizes the previous art of epothilone analogs as anti-proliferatives and does not rely on this aspect for novelty. Thus, the breadth of the claims as to encompassing epothilone analogs is not a proper basis upon which to allege non-enablement. The activity and use of epothilone analogs relied on for the invention is known to those of ordinary skill in the art. Instead, the invention is characterized, in part, by the conjugation of the epothilone with a linker-recognition unit. In this respect, the claim is not particularly broad since it specifies the positions of the linking L groups and the structure of the linkages and also the structure of the EG recognition units attached by the linking groups.
- State of the Prior Art - As admitted in the Office Action, epothilones are known as antiproliferatives and anti-tumor agents. This factor weighs heavily in support of enablement since it would not involve undue experimentation for one of ordinary skill in the art to use appellants' novel conjugate compounds in methods analogous to the known methods. There is no allegation in the Office action that the state of the prior art supports non-enablement.
- Nature of the Invention - As pointed out above, the nature of the invention lies, in part, on the conjugation of the epothilone with a linker-recognition unit and there is no allegation in the Office action that the nature of the invention supports non-enablement.
- Level of Ordinary Skill - The M.D. or Ph.D. skill level, admitted in previous Office actions, is a very high skill level which also weighs in favor of a finding of enablement. There is no allegation in the Office action that the level of ordinary skill supports non-enablement.

- Predictability in the Art - Appellants submit that the level of unpredictability is not particularly high given the admitted state of the prior art regarding epothilone analogs and the ability of one at a high level of skill in the art to analogously apply appellants conjugate compounds to the known uses of epothilones. The allegations of unpredictability based on the Nicolau reference are discussed above and that discussion is incorporated herein by reference. Further, the standard for enablement is not absolute predictability but only reasonable expectation of success; see In re Wright, 999 F.2d 1557, 27 USPQ2d 1510,1512 (Fed.Cir. 1993).
- Direction Provided by Inventor - As discussed above, the specification points out the known activity of epothilones and the specification exemplifies a number of particular diseases for which an antiproliferative effect is desired. The knowledge of one of ordinary skill in the art as to the antiproliferative effect of epothilone analogs is also applicable here. Further, there is no allegation in the Office action that this factor supports non-enablement.
- Existence of Working Examples - Although there are no working examples of methods of treatment in the disclosure, the law is clear that it is not necessary to provide working examples in order to enable the invention; see, e.g., In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970); and, In re Angstadt, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). The known antiproliferative effect of epothilone analogs makes confirmation of such known fact in this application unnecessary. Although unnecessary, the data provided in 132 Declaration filed herewith, support the activity of a epothilone analogs in assays which support their antiproliferative effect.
- Quantity of Experimentation Needed - Appellants respectfully submit that the quantity of experimentation needed is not excessive because the type of experimentation that one of ordinary skill in the art would need to conduct is only routine experimentation due to the known activity and uses of the epothilone analogs and the high level of skill in the art. That some experimentation is required does not support a finding of non-enablement; lack of enablement only arises when the experimentation required is undue. The initial action on the merits argued that there is no way to predict which compounds will be active. It may be true that it cannot be absolutely predicted a priori whether a particular compound will be

active, but absolute predictability is not required. As pointed out above, based on the knowledge in the art (and supporting data in the art and in the 132 Declaration) one of ordinary skill (a high level of skill here) in the art could reasonably expect that the epothilone analogs will exhibit an antiproliferative effect and would only need to conduct routine experimentation to determine such.

The above factors clearly balance in favor of the instant claims being enabled to one of ordinary skill in the art. There is no basis to suggest that one of ordinary skill in the art could not use appellants epothilone conjugate compounds in methods substantially analogously to methods in which known epothilone analog compounds are used.

For all of the above reasons, it is once again urged that the specification viewed in light of the knowledge of one of ordinary skill in the art (a high level of skill here) adequately teaches how to make and use the claimed invention. Thus, there exists ample basis to overturn the rejection under 35 U.S.C. §112, first paragraph.

In view of the above discussion, it is submitted that all rejections of record should be overturned and the application should be passed to issue. The same is respectfully requested.

Respectfully submitted,
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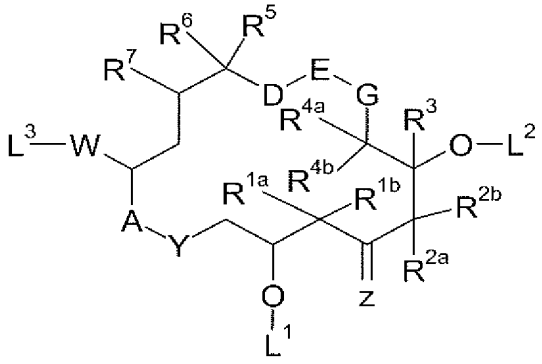
Date: October 16, 2007

(VIII) CLAIMS APPENDIX

1. A conjugate compound of formula (I):



I,

in which

R^{1a} and R^{1b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_m-$ group, in which m is 2 to 5,

R^{2a} and R^{2b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_n-$ group, in which n is 2 to 5, or C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl,

R^3 is hydrogen, C_1-C_{10} alkyl, aryl or aralkyl, and

R^{4a} and R^{4b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_p-$ group, in which p is 2 to 5,

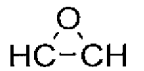
R^5 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, CO_2H, CO_2alkyl, CH_2OH, CH_2Oalkyl, CH_2Oacyl, CN, CH_2NH_2, CH_2N(alkyl, acyl)$_{1,2}$, or CH_2Hal,

Hal is a halogen atom,

R^6 and R^7, in each case, are hydrogen, or together an additional bond or together an oxygen atom, or together an NH group, or together an N-alkyl group, or together a CH_2 group, and

G is an oxygen atom or CH_2,

D-E is a group H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2,

CH_2-CH(OH),  , O-CH_2, or, if G represents a CH_2 group, is additionally CH_2-O,

W is a group C(=X)R^8, or a bi- or tricyclic aromatic or heteroaromatic radical,

L^3 is hydrogen, or, if a radical in W contains a hydroxyl group, optionally forms a group O-L^4 with the latter, or, if a radical in W contains an amino group, optionally forms a group NR^{25}-L^4 with the latter,

R^{25} is hydrogen or C_1-C_{10} alkyl,

X is an oxygen atom, or two OR^{20} groups, or a C_2-C_{10} alkylenedioxy group, which is straight-chain or branched, or H/OR^9, or a $CR^{10}R^{11}$ group,

R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen or CN, and

R^9 is hydrogen or a protective group PG^X,

R^{10} and R^{11}, in each case independently of one another, are hydrogen, C_1-C_{20} alkyl, aryl, or aralkyl, or together with a methylene carbon atom form a 5- to 7-membered carbocyclic ring,

Z is oxygen or H/OR^{12},

R^{12} is hydrogen or a protective group PG^Z,

A-Y is a group O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) or NR^{21}-SO_2,

R^{20} is C_1-C_{20} alkyl,

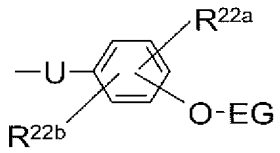
R^{21} is a hydrogen atom or C_1-C_{10} alkyl,

PG^X, PG^Y, and PG^Z are a protective group PG, and

L^1, L^2, L^4, independently of one another, are hydrogen, a group C(=O)Cl, a group C(=S)Cl, a group PG^Y or a linker-recognition unit of formula (III);

with the condition that at least one substituent L^1, L^2 or L^4 represents a linker-recognition unit of formula (III);

the linker-recognition unit of formula (III) has the following structure,



III,

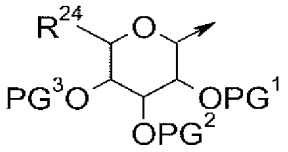
in which

R^{22a} and R^{22b}, independently of one another, are hydrogen, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy, aryl, aralkyl, hydroxy, alkoxy, CO_2H, CO_2alkyl, halogen, CN, NO_2, NH_2, or N_3,

U is $-C(=O)NR^{23}-$, $-C(=S)NR^{23}-$, $-C(=O)NR^{23}-CH_2-$, $-C(=S)NR^{23}-CH_2-$, $-C(=O)O-$, $-C(=S)O-$, $-C(=O)O-CH_2-$, or $-C(=S)O-CH_2-$,

R^{23} is hydrogen or C_1-C_{10} alkyl, and

EG is a recognition unit of formula (IV):



IV,

in which

R^{24} is a group CH_2OPG^4 or a group CO_2R^{26},

PG^1, PG^2, PG^3, and PG^4, independently of one another, are hydrogen or a protective group PG,

R^{26} is hydrogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_4-C_7 cycloalkyl, which can contain an oxygen atom, aryl, aralkyl, tris(C_1-C_{20} alkyl)silyl, bis(C_1-C_{20} alkyl)-arylsilyl, (C_1-C_{20} alkyl)-diarylsilyl, or tris(aralkyl)-silyl,

as a uniform isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof.

2. A conjugate compound according to claim 1, whereby:

A-Y represents O-C(=O) or NR^{21}-C(=O),

D-E represents an H_2C-CH_2 group or an HC=CH group,

G represents a CH_2 group,

Z represents an oxygen atom,

R^{1a} and R^{1b} in each case represent C_1-C_{10} alkyl or together a $-(CH_2)_p$ group with p equal to 2 or 3 or 4,

R^{2a} and R^{2b}, independently of one another, represent hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl,

R^3 represents hydrogen;

R^{4a} and R^{4b}, independently of one another, represent hydrogen or C_1-C_{10} alkyl;

R^5 represents hydrogen or C_1-C_4 alkyl or CH_2OH or CH_2NH_2 or $CH_2N(alkyl, acyl)_{1,2}$ or CH_2Hal,

R^6 and R^7 together represent an additional bond or together an NH group or together an N-alkyl group or together a CH_2 group or together an oxygen atom,

W represents a group $C(=X)R^8$ or a 2-methylbenzothiazol-5-yl radical or a 2-methylbenzoxazol-5-yl radical or a quinolin-7-yl radical or a 2-aminomethylbenzothiazol-5-yl radical or a 2-hydroxymethylbenzothiazol-5-yl radical or a 2-aminomethylbenzoxazol-5-yl radical or a 2-hydroxymethylbenzoxazol-5-yl radical,

X represents a $CR^{10}R^{11}$ group,

R^8 represents hydrogen or C_1-C_4 alkyl or a fluorine atom or a chlorine atom or a bromine atom, and

R^{10}/R^{11} represent hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl or hydrogen/2-methyloxazol-4-yl or hydrogen/2-aminomethylthiazol-4-yl or hydrogen/2-aminomethyloxazol-4-yl or hydrogen/2-hydroxymethylthiazol-4-yl or hydrogen/2-hydroxymethyloxazol-4-yl.

3. A conjugate compound according to claim 1, whereby:

R^{22a} and R^{22b} represent C_1-C_8-alkyl, C_1-C_8-alkoxy, halogen, nitro, CN, N_3, NH_2,

or CO_2-(C_1-C_8-alkyl).

4. A conjugate compound according to claim 1, whereby:

R^{26} represents C_1-C_8-alkyl or C_2-C_8-alkenyl.

5. A conjugate compound according to claim 1, whereby:

R^{2a} represents hydrogen and R^{2b} represents C_1-C_7-alkyl, C_2-C_7-alkenyl or C_2-C_7-alkinyl; or R^{2b} represents hydrogen and R^{2a} represents C_1-C_7-alkyl, C_2-C_7-alkenyl or C_2-C_7-alkinyl.

6. A conjugate compound according to claim 1, whereby:

R^{22a} and R^{22b} represent methyl, ethyl, propyl, i-propyl, *tert.*butyl, CF_3, C_2F_5, F, Cl, nitro, CN, N_3, NH_2, CO_2-methyl, CO_2-ethyl, CO_2-propyl or CO_2-i-propyl.

7. A conjugate compound according to claim 1, whereby:

R^{26} represents methyl, ethyl, propyl, i-propyl, t-butyl, CF_3, propenyl or butenyl.

8. A conjugate compound according to claim 1, whereby:

R^{2a} represents hydrogen, and R^{2b} represents methyl, ethyl, propyl, i-propyl, propenyl, butenyl, propinyl or butinyl; or R^{2b} represents hydrogen, and R^{2a} represents methyl, ethyl, propyl, i-propyl, propenyl, butenyl, propinyl or butinyl.

9. A conjugate compound according to claim 1, whereby the portion of the compound absent the linker-recognition unit of at least one of L^1, L^2 and L^3, is selected from the group that consists of:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-

7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-

methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-

chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

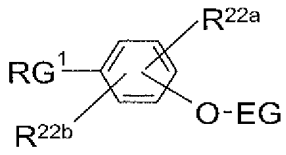
whereby the hydrogen atoms are replaced by radicals L^1-L^3 in the positions indicated in formula (I).

10. A conjugate compound according claim 1, whereby the conjugate contains more than one EG recognition unit, and whereby the recognition units are identical.

12. A process for the production of a conjugate compound according to claim 1, which comprises reacting:

a compound of formula (I), in which the substituents have the meanings that are mentioned in claim 1, but the condition that at least one substituent L^1, L^2, or L^4 represents a linker-recognition unit of formula (III) need not be met, and at least one substituent L^1, L^2, or L^4 represents hydrogen, a group C(=O)Cl or a group C(=S)Cl,

with a linker-recognition unit, which is selected from the group that consists of:
a linker-recognition unit of formula (III^1)



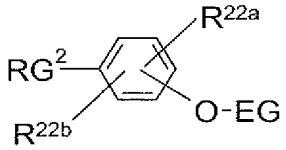
III^1,

in which

RG^1 represents an O=C=N group or an S=C=N group or an O=C=N-CH_2 group or an S=C=N-CH_2 group; and

R^{22a}, R^{22b} and EG have the meanings that are mentioned in claim 1; or

a linker-recognition unit of formula (III^2):



III²,

in which

RG^2 represents an HO-CH_2 group or an HNR^{23}-CH_2 group; and

R^{22a}, R^{22b} and EG have the meanings that are mentioned in claim 1;

but with the condition that the following compounds are not included:

(4-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(2-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(4-Hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(2-Hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(4-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside;

(2-Hydroxymethyl-4-nitro)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(4-Hydroxymethyl-2-nitro)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

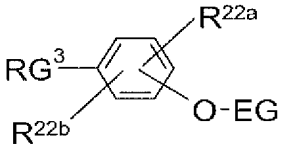
(2-Hydroxymethyl-4-nitro)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(4-Hydroxymethyl-2-nitro)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(2-Chloro-4-hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside; and

(2-Chloro-4-hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

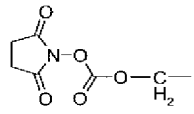
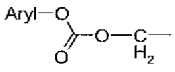
or a linker-recognition unit of formula (III^3):



III³,

in which

RG^3 represents a Hal-C(=O)-CH_2 group or a Hal-C(=S)-CH_2 group or an R^{27}-C(=O)-O-C(=O)-CH_2 group or an R^{27}-C(=O)-O-C(=S)-CH_2 group or a

 group or a  group;

R^{27} is C_1-C_{10} alkyl, aryl or aralkyl; and

R^{22a}, R^{22b} and EG have the meanings that are mentioned in claim 1;

but with the condition that the following compounds are not included:

2,5-Dioxopyrrolidin-1-yl-[4-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[4-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)-methyluronate)benzyl]carbonate;

4-Nitrophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-benzyl]carbonate;

4-Nitrophenyl-[2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-5-nitrobenzyl]carbonate;

4-Nitrophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate;

4-Nitrophenyl-[4-methoxy-5-nitro-2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)benzyl]carbonate;

4-Nitrophenyl-[4-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate; and

4-Chlorophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate.

23. A pharmaceutical or medication composition which comprises a conjugate compound according to claim 1 and a pharmaceutically acceptable carrier.

24. A method for treating a disease associated with proliferative processes in a patient which comprises administering to the patient an anti-proliferative effective amount of a conjugate compound of claim 1.

25. A method according to claim 24, wherein the disease is selected from the group consisting of tumor diseases, inflammatory diseases, neurodegenerative diseases, angiogenesis-associated diseases, multiple sclerosis, Alzheimer's disease and rheumatoid arthritis.

26. A method for treating a primary tumor and/or metastases that are not operatively accessible in a patient which comprises administering to the patient an effective amount of a conjugate compound of claim 1.

27. A method according to claim 26 whereby the conjugate compound is administered in combination with one or more other substances to trigger enhanced cell death (apoptosis) and necrosis.

28. A method according to claim 26 whereby the conjugate compound is administered in combination with one or more substances that is/are selected from the group consisting of an L19 construct, EDB-fibronectin and a combrestatin A4 prodrug.

29. A conjugate compound according to claim 1, wherein, in each instance, aryl is selected from the group consisting of phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, quinolyl, thiazolyl, benzothiazolyl, benzoxazolyl, which are optionally substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl, or C_1-C_{20}-acyloxy groups.

30. A conjugate compound according to claim 1, wherein the bi- or tricyclic aromatic or heteroaromatic radical for W is selected from the group consisting of naphthyl, anthryl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolyl, isoquinolyl, benzoxazinyl, benzofuranyl, indolyl, indazolyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thienopyridinyl, pyridopyridinyl, benzopyrazolyl, benzotriazolyl, or dihydroindolyl, which are optionally substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl, or C_1-C_{20}-acyloxy groups.

31. A conjugate compound according to claim 1, wherein the aralkyl groups, in each case, are selected from the group consisting of benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thienylethyl, and pyridylpropyl, which are optionally substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl, or C_1-C_{20}-acyloxy groups.

32. A conjugate compound according to claim 1, wherein the protective groups PG are each selected from: tris(C_1-C_{20} alkyl)silyl, bis(C_1-C_{20} alkyl)-arylsilyl, (C_1-C_{20} alkyl)-diarylsilyl, tris(aralkyl)-silyl, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_4-C_7-cycloalkyl which optionally contains an oxygen atom in the ring, aryl, C_7-C_{20}-aralkyl, C_1-C_{20}-acyl, aroyl, C_1-C_{20}-alkoxycarbonyl, C_1-C_{20}-alkylsulfonyl, arylsulfonyl or the
amino protective groups Alloc, Boc, Z, benzyl, f-Moc, Troc, Stabase or benzostabase.

33. A conjugate compound of claim 1, wherein m is 3 to 5.

(IX) EVIDENCE APPENDIX

Declaration by Ulrich Klar under 37 CFR §1.132, dated August 16, 2004.

(Follows)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Ulrich Klar et al.	:	Group Art Unit:1614
Serial No.: 09/485,292	:	Examiner: Binta Robinson
Filed: 3 May 2000	:	

For: NEW EPOTHIOLONE DERIVATIVES, PROCESS FOR THEIR PRODUCTION, AND THEIR PHARMACEUTICAL USE

132 DECLARATION

Sir:

I, Ulrich Klar, being duly warned, declare that:

I am an inventor identified in the above-captioned application and am familiar with the invention described therein and with the grounds alleged for rejection made against the claims of the application in the Office Action mailed 4 March 2004.

The following experiments were conducted by me or under my supervision to show the advantage of replacement of the 6-methyl group in the natural compounds Epothilone B and Epothilone D by an ethyl or other higher alkyl substituent. The data unexpectedly demonstrate that the compounds with ethyl or other higher alkyl substituents have significantly better activity (i.e., lower IC_{50}) in more tumor cell lines and better sensitivity to the multi-drug-resistant cell line NCI/ADR compared to MCF-7 than the corresponding compounds with methyl substitution.

The tumor cell lines used for the in vitro assays are of human origin. It is well accepted in the scientific community that the inhibition of tumor cell proliferation especially of different tumor cell lines of one tumor type (e.g. breast, lung, ovary etc.) are an indication that the compound may be useful in the treatment of this type of cancer also in vivo. Because not all of these tumor cell lines grow in vivo and due to our animal protecting laws, in vivo experiments can be performed only for a very limited number of compounds which are selected upon their in vitro profile.

In the following overview the unexpected beneficial effects observed by replacing the 6(10)-methyl group present in all naturally occurring epothilones by an alkyl-group is demonstrated.

The following data would demonstrate to the normally skilled researcher in this technology that the ethyl and higher alkyl compounds have significantly advantageous properties compared to the corresponding methyl compounds.

1. Effect on activity

Compared are the IC_{50} values obtained for different human tumor cell lines of a 6(10)-alkyl compound (right columns) with its corresponding 6(10)-methyl reference compound (middle columns). To demonstrate the broad usefulness of these unexpected findings, different types of epothilones are listed in Tables 1 to 4 as examples. Beside the naturally occurring epothilone B (Table 1) and epothilone D (Table 2) also synthetic analogs bearing several structural modifications at different regions of the molecule were investigated (Tables 3 to 4). The data unexpectedly demonstrate that the replacement of the 6(10)-methyl group by an alkyl group in different types of epothilones enhances the antiproliferative activity (lower IC_{50} values).

Table 1: Replacement of the 6-methyl group in the natural compound Epothilone B by an ethyl group enhances the activity.

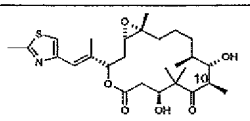
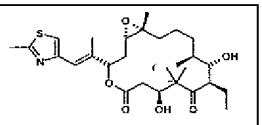
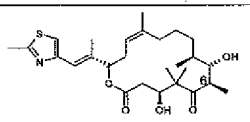
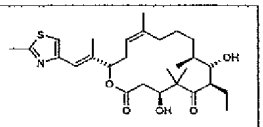
Table 1	 Epothilone B (Ref. 1)	
MCF-7	0.59 nM	< 0.24 nM
NCI/ADR	3.5 nM	0.43 nM
MaTu	0.46 nM	< 0.24 nM
MaTu/ADR	1.2 nM	< 0.19 nM
A 431	0.43 nM	< 0.1 nM
H460	0.35 nM	< 0.1 nM

Table 2: Replacement of the 6-methyl group in the natural compound Epothilone D by an ethyl group enhances the activity.

Table 2	 Epothilone D (Ref. 1)	

MCF-7	19 nM	4.4 nM
MaTu	13 nM	6.3 nM
MaTu/ADR	37 nM	5.8 nM

Table 3: Replacement of the 6-methyl group in the synthetic reference compound 3 by a hydroxy-butyl group enhances the activity.

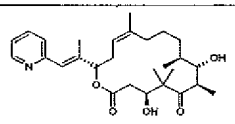
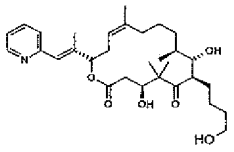
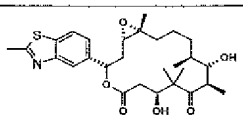
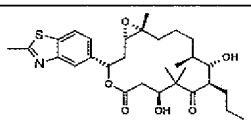
Table 3	 (Ref. 3)	
MCF-7	5.6 nM	3.5 nM
MaTu	5.4 nM	2.3 nM

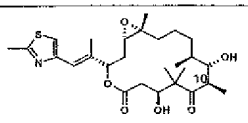
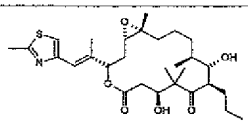
Table 4: Replacement of the 6-methyl group in the synthetic reference compound 4 by a propyl group enhances the activity.

Table 4	 (Ref. 4)	
MaTu	0.44 nM	0.2 nM
MaTu/ADR	0.81 nM	0.58 nM

2. Effect on overcoming multi-drug-resistance

Beside the overall activity it is desired not to lose activity against such human tumor cells which had already acquired marked resistancies. In Tables 5 to 10 the effect of replacing the 6(10)-methyl group by an alkyl group in different types of epothilones on the relative sensitivity to a human tumor cell lines overexpressing the multidrug resistance (MDR) phenotype is discussed. The relative sensitivity is defined as quotient of the IC_{50}-values of a parent human tumor cell line (MCF7 or MaTu) and its corresponding MDR cell line (NCI/ADR or MaTu/ADR). This quotient is set to 100% for the reference compound bearing the 6(10)-methyl group. A value above 100% for the 6(10)-alkyl compound therefore indicates an improved sensitivity of the compound against the MDR cell line compared to its corresponding 6(10)-methyl reference compound.

Table 5: Replacement of the 6-methyl group in the natural compound Epothilone B by a propyl group enhances the relative sensitivity by 353%.

Table 5	 Epothilone B (Ref. 1)	
MCF-7	0.59 nM	3.4 nM

NCI/ADR	3.5 nM	4.3 nM
Ratio MCF7:NCI/ADR	0.17 (100%)	0.77 (453%)

Table 6: Replacement of the 6-methyl group in the natural compound Epothilone D by a propyl group enhances the relative sensitivity by 32% and 114%, respectively.

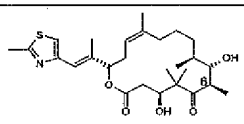
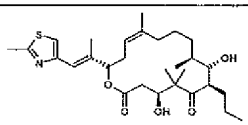
Table 6	 Epothilone D (Ref. 2)	
MCF-7	19 nM	38 nM
NCI/ADR	50 nM	76 nM
Ratio MCF7:NCI/ADR	0.38 (100%)	0.5 (132%)
MaTu	13 nM	36 nM
MaTu/ADR	37 nM	48 nM
Ratio MaTu:MaTu/ADR	0.35 (100%)	0.75 (214%)

Table 7: Replacement of the 6-methyl group in the synthetic reference compound 7 by an ethyl group enhances the relative sensitivity by 208% and 186%, respectively.

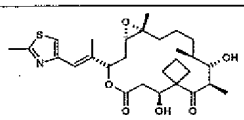
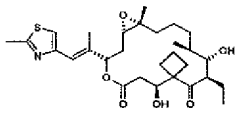
Table 7	 (Ref. 7)	
MCF-7	0.47 nM	1.6 nM
NCI/ADR	3.6 nM	4 nM
Ratio MCF7:NCI/ADR	0.13 (100%)	0.4 (308%)
MaTu	0.46 nM	1.2 nM
MaTu/ADR	1.3 nM	1.2 nM
Ratio MaTu:MaTu/ADR	0.35 (100%)	1.0 (286%)

Table 8: Replacement of the 6-methyl group in the synthetic reference compound 3 by an ethyl or propyl group enhances the relative sensitivity by 147% or 68%, respectively.

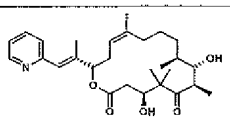
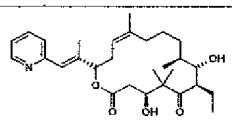
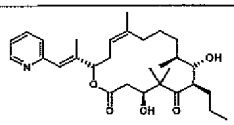
Table 8	 (Ref. 3)		
MCF-7	5.6 nM	23.5 nM	26 nM
NCI/ADR	29 nM	50 nM	81 nM
Ratio MCF7:NCI/ADR	0.19 (100%)	0.47 (247%)	0.32 (168%)

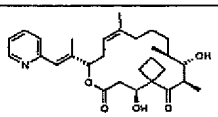
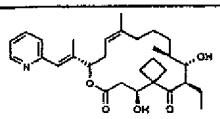
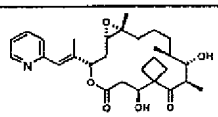
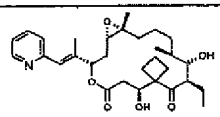
Table 9	 (Ref. 8)	
MCF-7	22 nM	33 nM
NCI/ADR	56 nM	28 nM
Ratio MCF7:NCI/ADR	0.39 (100%)	1.18 (303%)
MaTu	8.8 nM	31 nM
MaTu/ADR	29 nM	41 nM
Ratio MaTu:MaTu/ADR	0.30 (100%)	0.76 (253%)

Table 10: Replacement of the 6-methyl group in the synthetic reference compound 9 by an ethyl group enhances the relative sensitivity by 1592%.

Table 10	 (Ref. 9)	
MaTu	0.49 nM	1.1 nM
MaTu/ADR	4.1 nM	0.54 nM
Ratio MaTu:MaTu/ADR	0.12 (100%)	2.03 (1692%)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Ulrich Klar 16.08.2004

Ulrich Klar Date

(X) RELATED PROCEEDINGS APPENDIX

(None)

(XII) Appendix of Comments to Pre-Appeal Conferees

(None)